VIP Cross-Coupling **Very Important Paper**

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Ligand-Promoted Oxidative Cross-Coupling of Aryl Boronic Acids and Aryl Silanes by Palladium Catalysis**

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Abstract: *The first cross-coupling reaction between aryl silanes and aryl boronic acids is described. This transformation represents one of the very few examples of coupling reactions between two nucleophilic organometallic reagents and provides a new method for the formation of biaryl compounds. The successful development of this reaction was enabled by the use of commercially available 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) as the ligand. A small amount of BINAP (3 mol%) was sufficient to suppress the formation of the homocoupling products, and the reaction yielded the cross-coupling products with high selectivity under mild conditions, even when the ratio of the two coupling partners was 1:1.*

Transition-metal-catalyzed C−C bond-forming reactions are among the most widely used transformations in organic synthesis.[1] Cross-coupling reactions of organic electrophiles (generally aryl or alkyl (pseudo)halides) and organometallic nucleophiles have proven to be particularly versatile.[2] A range of such reactions have been developed thus far, including Suzuki,[3] Negishi,[4] Stille,[5] Hiyama,[6] and Kumada[7] reactions. Aside from traditional cross-coupling reactions between a nucleophile and an electrophile (Figure 1a), the reductive coupling of two electrophiles (Figure 1b) and the oxidative coupling of two nucleophiles (Figure 1c) represent two alternative reaction manifolds through which cross-coupling can be achieved.[8] It should also be mentioned that a new type of oxidative coupling, which involves the reaction of C−H bonds, has recently attracted considerable interest.[9]

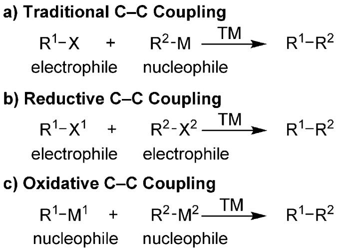

Figure 1. Transition-metal-catalyzed cross-coupling reactions. M = metal, TM = transition metal, X = leaving group.

The vast majority of research on such transformations has focused on traditional cross-coupling processes, and the latter two reaction types have remained comparatively underdeveloped. The major challenge in reductive and oxidative cross-coupling is the chemoselectivity.[8a] Unlike traditional cross-couplings, these two reaction types involve two coupling partners of the same type (either two electrophiles or two nucleophiles). As such, undesired homocoupling tends to compete with cross-coupling, and it is often challenging to achieve high selectivity for the desired cross-coupled product. Whereas several examples of reductive cross-coupling processes have been reported,[10] oxidative cross-couplings have proven to be more challenging, with the majority of the oxidative coupling reactions restricted to homocoupling rather than cross-coupling.[8,11] However, several excellent cross-coupling reactions of two organometallic compounds that proceed with high chemoselectivity have been reported. An early example is the oxidation of mixed aryl cuprates reported by Lipshutz and co-workers (Figure 2a).[12] Subsequently, the Knochel group described the oxidative coupling of lithium aryl/alkenyl cuprates with alkynyl lithium reagents (Figure 2a).[13] Significantly, palladium-catalyzed cross-couplings of alkyl zinc reagents with alkynylstannanes were achieved by the Lei group, and the method was successfully extended to the reaction of aryl zinc and alkyl indium reagents (Figure 2b).[14] The Cahiez group reported iron- and manganese-catalyzed selective couplings of two different organozinc or organomagnesium reagents (Figure 2c,d).[15] Furthermore, Hirao and co-workers disclosed a series of

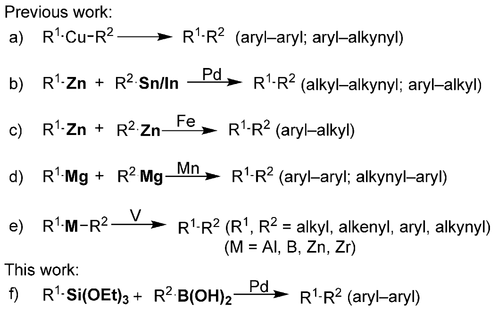

Figure 2. Transition-metal-mediated/catalyzed oxidative cross-coupling reactions of two organometallic nucleophiles.

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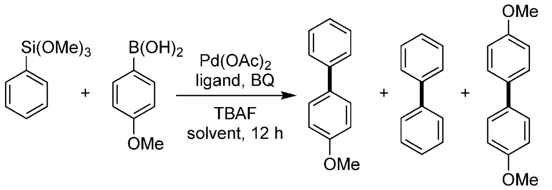
oxovanadium(V)-mediated/catalyzed ligand coupling reactions of main-group organometallic compounds (Figure 2e).[16]

Considering the utility of biaryl-forming reactions,[17] we set out to develop oxidative cross-coupling reactions of two aryl metal reagents. To achieve high selectivity for the cross-coupling pathway in an oxidative coupling reaction, two strategies could be envisioned: 1) using two different metals or 2) utilizing two coupling partners with organic fragments that have distinct innate reactivity. In the context of biaryl synthesis, the former would be anticipated to lead to a more versatile reaction. In terms of reaction design, we were attracted to organoboron and organosilicon coupling partners because of their favorable properties, such as relatively high stability, low toxicity, and broad functional-group tolerance.[18] Herein, we report the first example of a palladium-catalyzed oxidative cross-coupling between aryl boronic acids and aryl silanes with BINAP as the ligand (Figure 2f).

We initiated this research project by investigating the cross-coupling of trimethoxyphenylsilane (**1a**) and 4-methoxyphenylboronic acid (**2a**). Unlike traditional Pd^0-catalyzed cross-coupling reactions between an electrophile and a nucleophile, oxidative cross-couplings require the use of a terminal oxidant to reoxidize Pd^0 to Pd^{II} to close the catalytic cycle.[14a] 1,4-Benzoquinone (BQ) is commercially available and inexpensive, so it is a convenient oxidant.[19] Selected examples of reaction conditions that were surveyed are shown in Table 1; we focused primarily on the effect of different ligands, oxidants, bases, and solvents. In the absence of a ligand, neither the homocoupling nor the cross-coupling products were observed in meaningful quantities. In the presence of PPh$_3$ (10 mol%), the desired cross-coupled product **3aa** was formed in 25% yield, along with products **4aa** and **5aa** from the homocoupling of **1a** and **2a**, respectively. Many other commonly used mono- and bidentate phosphine ligands led to similar outcomes. Gratifyingly, unlike other phosphines, BINAP was uniquely effective in promoting the cross-coupling in high yield (63%) while suppressing the yield of homocoupling product **4aa** (9%; entry 6). The yield of **3aa** decreased dramatically when a representative bidentate nitrogen-containing ligand, namely 1,10-phenanthroline, was employed instead of BINAP (entry 7). Notably, the yield and product distribution remained essentially unchanged when the amount of BINAP was reduced from 10 mol% to 5 or 3 mol% (entries 8 and 9). DMA and NMP were identified as optimal solvents (entries 10 and 11), and ultimately the yield was improved to 82% by fine-tuning the reaction temperature, the amounts of BQ and TBAF used, and the concentration (entries 12–14). Replacing BINAP with PPh$_3$ (3 or 6 mol%) under otherwise unchanged conditions resulted in a low yield of **3aa** and the formation of a large quantities of **4aa** (entries 15 and 16). Intriguingly, the identity of the ligand appears to have little impact on the formation of **5aa**, which was formed in low yields in all of the reactions that we performed.

Table 1: Optimization of the reaction conditions for the oxidative cross-coupling of aryl boronic acids and aryl silanes.



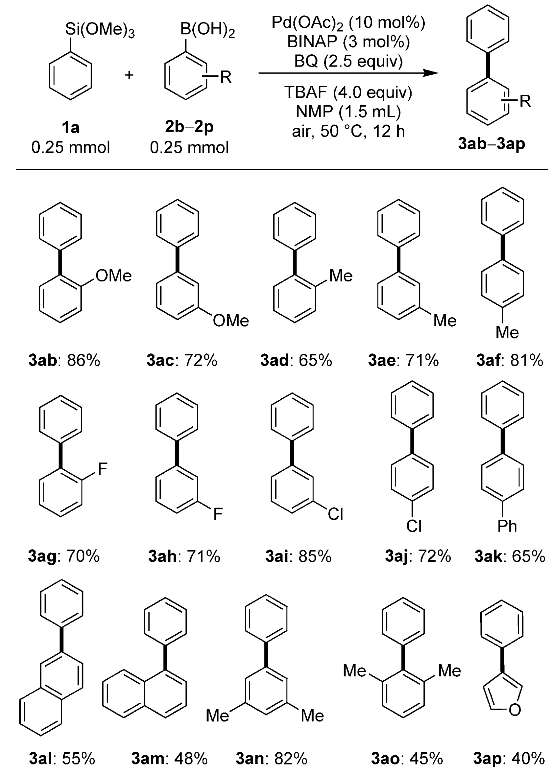
1a **2a** **3aa** **4aa** **5aa**

Entry	Ligand (mol%)	Solvent	**3aa** [%][b]	**4aa** [%][c]	**5aa** [%][c]	**3aa/4aa/5aa**
1	–	DMF	trace	–	–	–
2	PPh$_3$ (10)	DMF	25	36	8	1.4:1:0.22
3	TFP (10)	DMF	23	42	6	1.1:1:0.14
4	DPPP (10)	DMF	25	50	7	1:1:0.14
5	Xantphos (10)	DMF	28	48	6	1.2:1:0.13
6	BINAP (10)	DMF	63	9	8	14:1:0.9
7	phen (10)	DMF	16	37	3	0.86:1:0.08
8	BINAP (5)	DMF	64	9	8	14.2:1:0.9
9	BINAP (3)	DMF	65	9	6	14.4:1:0.67
10	BINAP (3)	DMA	68	9	5	15.1:1:0.6
11	BINAP (3)	NMP	72	8	6	18:1:0.75
12[d]	BINAP (3)	NMP	73	9	6	16.1:1:0.67
13[d,e]	BINAP (3)	NMP	77	8	5	19.3:1:0.63
14[d,e,f]	BINAP (3)	NMP[g]	82	8	5	20.5:1:0.63
15[d,e,f]	PPh$_3$ (3)	NMP[g]	26	39	6	1.33:1:0.15
16[d,e,f]	PPh$_3$ (6)	NMP[g]	26	38	6	1.37:1:0.16
17[d,e,f,h]	BINAP (3)	NMP[g]	60	12	9	12:1:0.75
18[d,f,i]	BINAP (3)	NMP[g]	36	6	12	12:1:2
19[d,f,j]	BINAP (3)	NMP[g]	trace	–	trace	–
20[d,e,f,k]	BINAP (3)	NMP[g]	–	–	–	–

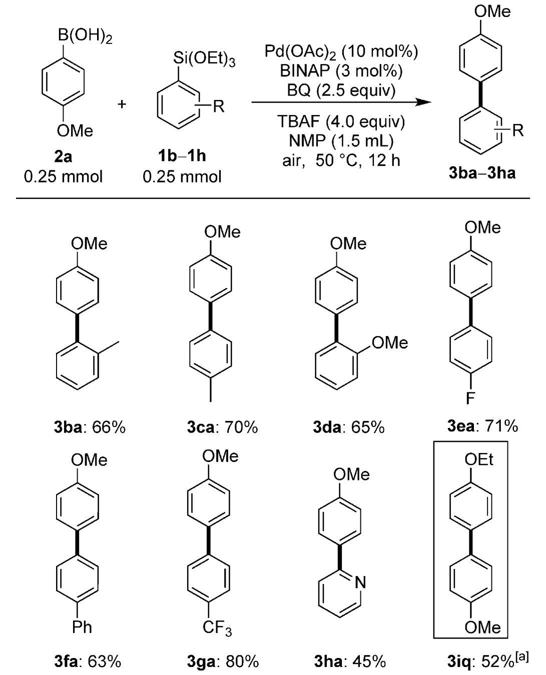
[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.25 mmol), Pd(OAc)$_2$ (10 mol%), ligand, BQ (2 equiv), TBAF (3 equiv), solvent (1 mL), 75 °C, 12 h. [b] Yields of isolated products. [c] Yields determined by ^{1}H NMR analysis of the crude reaction mixture using CHCl$_2$CHCl$_2$ as an internal standard. Yields were calculated based on the fact that two molecules of **1a** or **2a** form one molecule of **4aa** or **5aa.** [d] 50 °C. [e] BQ (2.5 equiv). [f] TBAF (4 equiv). [g] Solvent (1.5 mL). [h] N$_2$ atmosphere. [i] BQ (0.2 equiv), O$_2$ atmosphere. [j] No BQ. [k] No Pd(OAc)$_2$. BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, DMA = *N*,*N*-dimethylacetamide, DMF = *N*,*N*-dimethylformamide, DPPP = 1,3-bis(diphenylphosphino)propane, NMP = *N*-methylpyrrolidone, phen = phenanthroline, TBAF = tetrabutylammonium fluoride, TFP = tri(2-furyl)phosphine, Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

When the reaction was carried out under nitrogen atmosphere, **3aa** was observed in 60% yield (entry 17), and only trace amounts of any of the three products were found in the absence of BQ (entry 19). The former result suggests that O$_2$ may be involved in catalyst reoxidation, whereas the latter implies that BQ plays another role beyond serving as an oxidant in the reaction. It is well known that BQ can accelerate reductive elimination,[9a] and it may indeed do so in this transformation. Attempts to reduce the amount of BQ in the presence of O$_2$ resulted in a much lower yield (entry 18). Finally, no coupling products were observed in the absence of Pd(OAc)$_2$ (entry 20).

Having developed an efficient procedure for the Pd-catalyzed cross-coupling of trimethoxyphenylsilane and 4-methoxyphenylboronic acid, we next investigated the substrate scope of this transformation. We first examined the performance of a variety of aryl boronic acids under the optimized reaction conditions. Thus, as shown in Scheme 1, *ortho*- and *meta*-methoxyphenylboronic acid underwent the cross-coupling with **1a** in 86% and 72% yield, respectively.



Scheme 1. Variation of the aryl boronic acid. Yields are those of purified and isolated products.



Scheme 2. Variation of the aryl silane. Yields are those of purified and isolated products. [a] The cross-coupling product from triethoxy(4-methoxyphenyl)silane (**1i**) and 4-ethoxyphenylboronic acid (**2q**). The product was obtained as an inseparable mixture of cross-coupling product **3iq** and homocoupling products 4,4′-diethoxybiphenyl (**5qq**) and 4,4′-dimethoxybiphenyl (**4ii**). **3iq**/**5qq**/**4ii** = 18.5:2.3:1.0.

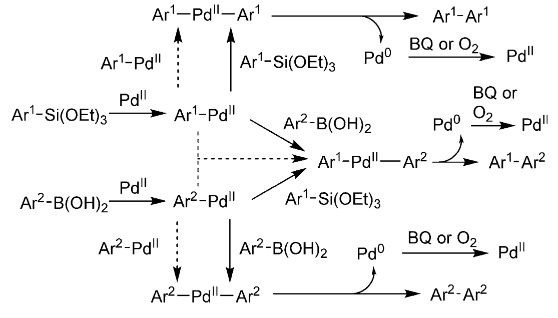
Aryl boronic acids containing methyl groups were also reactive. The presence of a methyl group at the *ortho* position led to the lowest yield, presumably because of steric hindrance. Both fluoro and chloro groups were tolerated in the reaction, giving the desired cross-coupled products in high yields. Boronic acids derived from biphenyl and naphthalene were also suitable. Sterically hindered 2,6-dimethylphenylboronic acid underwent the cross-coupling reaction successfully, albeit in a far lower yield than its 3,5-dimethyl analogue. One heteroaryl boronic acid was also examined, and 3-furanylboronic acid was found to be compatible with the reaction conditions, giving 3-phenylfuran as the cross-coupled product.

Next, the aryl silane component was varied using 4-methoxyphenylboronic acid as the coupling partner (Scheme 2). It was found that aryl silanes bearing electron-donating methyl or methoxy groups were suitable coupling partners. Furthermore, fluoro and trifluoromethyl groups were well-tolerated, as were biphenyl and 2-pyridyl substituents.

Notably, when triethoxy(4-methoxyphenyl)silane (**1i**) and 4-ethoxyphenylboronic acid (**2q**), which contain two similar aryl groups, were subjected to the standard conditions, the reaction still predominantly yielded the cross-coupled product (**3iq**; Scheme 2). This result indicates that the high selectivity for the cross-coupling likely arises from the different reactivities of the two metal centers, rather than from different properties of the two aryl groups.

Mechanistically, the reaction starts with transmetalation of Pd^{II} with either the aryl silane or the aryl boronic acid (Scheme 3). In one mechanistic scenario (bold arrows), the resulting $\{Pd^{II}(Ar)\}$ species undergoes a second transmetalation to form $\{Pd^{II}(Ar^1)(Ar^2)\}$, and reductive elimination generates the biaryl product and a Pd^0 complex. Subsequently, the Pd^0 species is oxidized to Pd^{II} by BQ or O_2 to close the catalytic cycle. Homocoupling products are formed following analogous pathways.

An alternative pathway for this coupling reaction involves a "bimetallic" mechanism (dashed arrows),[20] in which the $\{(Ar^1)Pd^{II}(Ar^2)\}$ species is formed by transmetalation between two organopalladium species, $\{Pd^{II}(Ar^1)\}$ and $\{Pd^{II}(Ar^2)\}$. However, as the reaction between two coupling partners containing two similar aryl groups (**1i** and **2q**) still predominantly yielded the cross-coupled product (**3iq**; Scheme 2), the bimetallic mechanism should be ruled out. If the bimetallic mechanism was operating, the transmetalation



Scheme 3. Proposed mechanisms for the formation of the cross-coupling and homocoupling products.

rates of {(Ar^1)Pd^{II}} and {(Ar^2)Pd^{II}}, {(Ar^1)Pd^{II}} and {(Ar^1)Pd^{II}}, and {(Ar^2)Pd^{II}} and {(Ar^2)Pd^{II}} should be almost equal, because Ar^1 and Ar^2 are very similar. Likewise, the reductive elimination rates of {(Ar^1)Pd^{II}(Ar^2)}, {(Ar^1)Pd^{II}-(Ar^1)}, and {(Ar^2)Pd^{II}(Ar^2)} should also be very similar. As a consequence, no preferential formation of the cross-coupling products could be observed, which contradicts the experimental results.

In summary, whereas traditional cross-coupling reactions of nucleophiles with electrophiles have been extensively studied, the oxidative cross-coupling of two nucleophiles has remained underdeveloped. We have now reported a new method for the cross-coupling of aryl trialkoxysilanes and aryl boronic acids. To the best of our knowledge, this palladium-catalyzed reaction is the first example of a cross-coupling between organosilanes and organoboron reagents, and it also represents one of the few methods for the formation of biaryl compounds from two nucleophilic organometallic reagents. The successful development of this reaction can be attributed to the use of commercially available BINAP as the ligand and inexpensive BQ as the oxidant. Notably, a small amount of BINAP (3 mol%) is sufficient to allow the reaction to take place under mild conditions. This transformation routinely forms the cross-coupled products with high selectivity, even when the ratio of the two coupling partners is 1:1. Further studies towards improving our understanding of the reaction mechanism and applying this type of reactivity for other processes are underway in our laboratory.

Keywords: cross-coupling · ligands · organoboron compounds · organosilicon compounds · palladium catalysis

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